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Cell specific reactivation of epicardium at the origin of fibro-fatty remodeling of the atrial myocardium

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Background & Purpose. Atrial fibrillation (AF) is often associated with an atrial cardiomyopathy, with fibro-fatty infiltrations of the sub-epicardium as an important component. We previously reported that epicardium-derived cells (EPDCs) can differentiate into adipocytes contributing to fat depot. Here, we examined if fibroblasts can also derived from EPDCs and contribute to the fibrotic remodeling of atrial subepicardium.

Methods. Samples of human right atria obtained during routine cardiac surgery were used for histological study and to harvest EPDCs. Clinical and histological data were analyzed using generalized linear models. A model of ischemic heart failure and atrial cardiomyopathy was created in rats and in a genetic lineage tracing WT1CreERT2+/−/Rosa-tdT+/- mice to follow. Primary cell culture models was used to study EPDC differentiation. Flow cytometry assays and single cell sequencing were used to characterize subpopulations of EPDCs.

Results. In human atria, epicardium could be composed of a thin cell monolayer in contact with myocardium or adipose tissue or could be a thick layer in continuity with dense fibro-fatty infiltrates. The latter aspect predominated in old patient (>70 year) with valve mitral diseases or in AF, clinical conditions associated with an atrial cardiomyopathy. Indeed, one week after the onset of the atrial remodeling, epicardium was already thick and fibrotic both in rat and mouse. Cells co-expressing markers of epicardial progenitors and fibroblasts were detected in the subepicardium of diseased atria both in human and murine. Moreover, a number of myo/fibroblasts from WT1CreERT2+/−/Rosa-tdT+/- mice were detected in diseased atria attesting of their epicardial origin. Distinct EPDC clusters were detected from cells harvested from epicardium whereas only PDGFRa-positive cells could differentiated into fibroblasts.

Conclusions. Epicardium activation is an early event during atrial remodeling, and is a source of fibroblasts contributing to fibro-fatty remodeling. Epicardium regulates the balance between adipose expansion and fibrosis accumulation and appears as a key determinant of atrial cardiomyopathy progression.